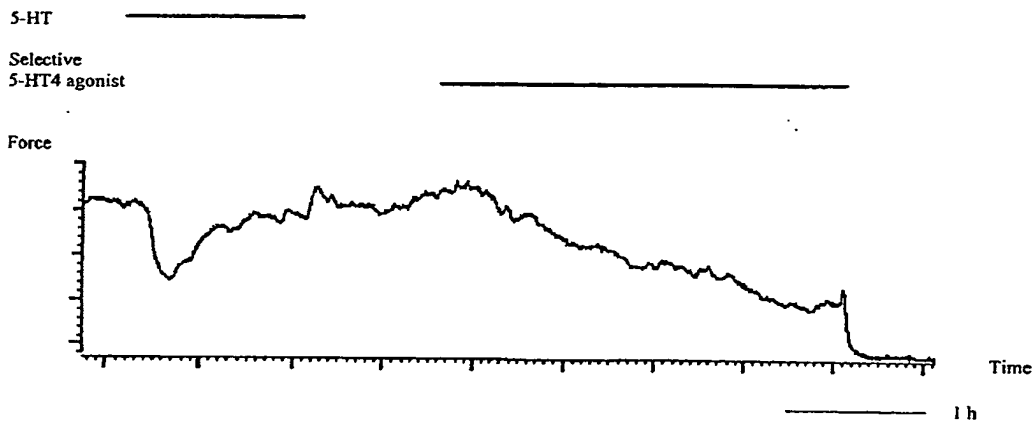




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(54) Title: MEDICAMENT



(57) Abstract

The present invention relates to a compound having agonist activity to the 5-HT₄ receptor for use as a medicament and to the use of said compounds in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compounds are administered. The present invention also relates to a compound having antagonist activity to the 5-HT_{2a} receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compounds are administered.

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MEDICAMENTField of the Invention

The present invention relates to a compound having agonist activity to the 5-HT₄ receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compound is administered. The present invention also relates to a compound having antagonist activity to the 5-HT_{2a} receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compound is administered.

Background of the Invention

Receptors of the 5-HT (serotonin; 3-(β -aminoethyl)-5-hydroxyindole) type are well known and occur throughout the body, e.g. in the airways, and their relevance has mainly been reported in conjunction with treatment of CNS, muscle and gastric disorders, as disclosed in e.g. WO 98/18458 and US 5 246 935. In such treatments, compounds having agonist activity to a 5-HT₁ type receptor are often used. As examples of other 5-HT receptors, mention can be made of receptors of the 5-HT₂, 5-HT₄, 5-HT₅, 5-HT₆ and 5-HT₇ type. For a recent review of 5-HT receptors, see Gerhardt, C.C., van Heerikhuizen, H., *Eur. J. Pharm.*, 334, 1-23 (1997), which is incorporated herein by reference.

Receptors of the 5-HT₂ type are also well known, e.g. through US 5 869 497, US 5 705 519 and US 5 246 935. The relevance of receptors of the 5-HT₂ type has been reported in conjunction with e.g. CNS and neuronal disorders. Such disorders are often treated with compounds having antagonist activity to a receptor of the 5-HT_{2a},

5-HT_{2B} or 5-HT_{2C} type. Examples of such compounds are ri-
tanserin and naftidrofuryl. A review of typical agonists
and antagonists of various 5-HT receptors is disclosed in
R.A. Glennon, Neuroscience and Biobehavioral Reviews, 14,
5 35-47 (1990), the whole content of which is incorporated
herein by reference.

SU 1 701 320 A1 discloses the use of serotonin for
treatment of acute asthma attacks. This reference does
not suggest any receptor mechanism for serotonin, which
10 is a compound with both a contracting and a relaxing ef-
fect on the airways, as is further discussed herein be-
low.

In the RBI Handbook of Receptor Classification and
Signal Transduction, 3rd Edition, 1998, RBI, One
15 Strathmore Road, Natick, MA 01760-2447, USA, Editor:
Keith J. Watling are compounds having agonist or antago-
nist activity to various receptors disclosed.

Disclosure of the Invention

The present invention is based on the novel finding
20 that certain 5-HT receptors are of utmost importance in
regulating bronchocontraction. In summary, it is dis-
closed herein that compounds having agonist activity to
the 5-HT₄ receptor bring about a bronchorelaxing action
upon administration thereof, and are therefore suitable
25 as agents for treatment of bronchocontraction disorders.
It is also disclosed herein that compounds having antago-
nist activity to the 5-HT₂, especially
5-HT_{2a}, receptor, are suitable agents in the treatment of
bronchocontraction disorders. Methods for treatment of
30 bronchocontraction disorders are also disclosed.

As used herein, the expression bronchocontraction
disorder refers to an abnormal increase of the force de-
velopment of the smooth muscle, resulting in a reduced
diameter in some or all of the airways of the lungs and/-
35 or the extrapulmonary airways. Said expression also re-
fers to reduction of airflow caused by swelling, oedema,

plasma extravasation or mucous secretion caused by e.g. asthma or any other disorder related thereto.

Accordingly, the present invention relates, in one of its aspects, to a compound having agonist activity to the 5-HT₄ receptor for use as a medicament. In another aspect it relates to use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving bronchocontraction, such as asthma.

In a preferred embodiment, the invention relates to the use of a compound having agonist activity to the 5-HT₄ receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said agonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

The present invention also relates, in another aspect, to a compound having antagonist activity to the 5-HT_{2a} receptor for use as a medicament. In another aspect it relates to use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving bronchocontraction, such as asthma.

In a preferred embodiment, the invention relates to the use of a compound having antagonist activity to a 5-HT_{2a} receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said antagonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

Said bronchocontraction may also occur in conjunction with such disorders as e.g. emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depres-

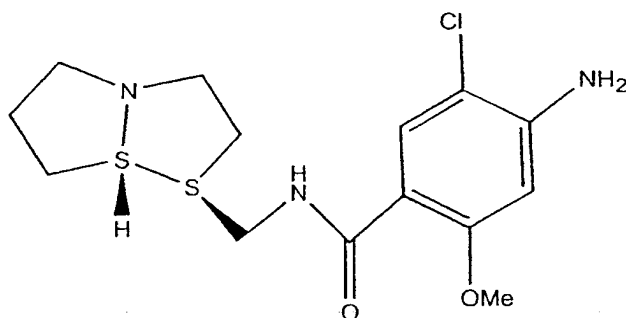
sion, anorectic or bulimic eating disorders, anxiety or various psychotic conditions, including schizophrenia.

The present invention also relates to the use of a compound having antagonist activity to a 5-HT_{2a} receptor in combination with a compound having agonist activity to the 5-HT₄ receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction. In a preferred embodiment said compound having agonist activity is serotonin or a derivative thereof having agonist activity to the 5-HT₄ receptor. This combination of the 5-HT_{2a} receptor antagonist and the agonist increases the serotonin transmission in the body, particularly in the presence of a serotonin uptake inhibitor (SRI). Further, the compounds having agonist activity to the 5-HT₄ receptor to be used according to the present invention are also useful in the present combination embodiment. In particular, said medicament is intended for treatment of asthma and disorders related thereto.

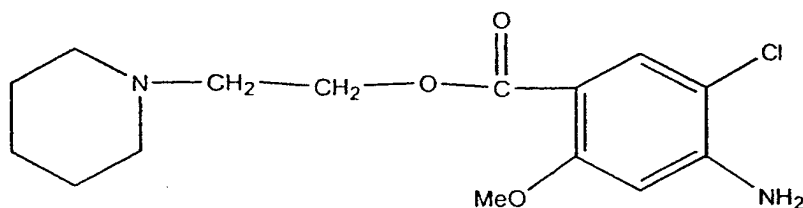
According to the present invention several known substances are, surprisingly, able to stimulate the 5-HT₄ receptor, without activating the contracting 5-HT_{2a} receptor, thereby generating a relaxing effect on the bronchocontraction. Such agonist compounds are selected from the group comprising the substances SC 53116, ML 10302, RS 67506 and BIMU 8, which are defined below, as well as the more unspecific 5-carboxamidotryptamine, and derivatives and pharmaceutically acceptable salts thereof having the same or essentially the same relaxation effect.

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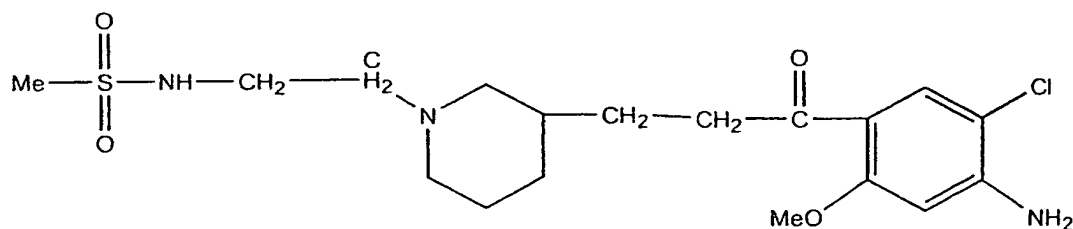
The invention also relates to the use of one or more of the above-mentioned agonist compounds: SC 53116, i.e. 4-amino-5-chloro-N-[[1S, 7aS)-hexahydro-1H-pyrrolizin-1-yl)methyl]-2-methoxy-benzamide, having the structural
5 formula:



ML 10302, i.e. 4-amino-5-chloro-2-methoxy-benzoic acid-2-(1-piperidinyl)ethylester, having the structural
10 formula:

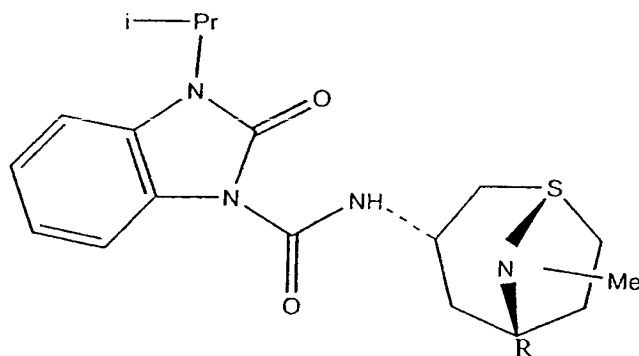


15 RS 67506, i.e. N-[2-[4-[3-(4-amino-5-chloro-2-methoxyphenyl)-3-oxopropyl]-1-piperidinyl]ethyl]-methanesulfonamide monohydrochloride, having the structural formula:



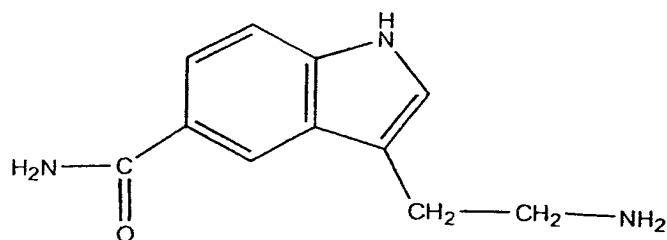
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BIMU 8, i.e. 2,3-dihydro-N-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-3-(1-methylethyl)-2-oxo-1H-benzimidazole-1-carboxamide monohydrochloride, having the structural formula:



5

5-carboxamidotryptamine, having the structural formula:



10

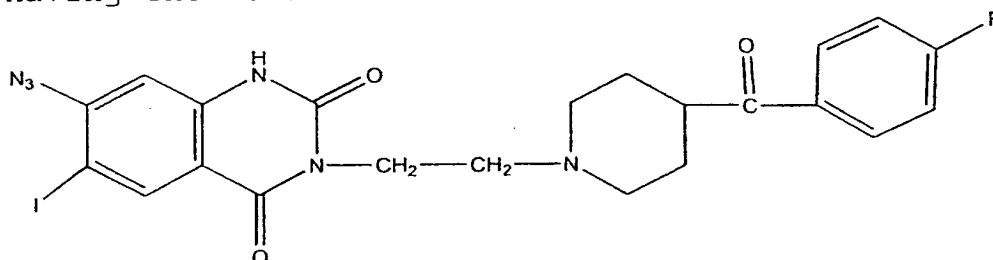
BIMU 1, BIMU 8, BRL 24924, Cisapride, DAU 6236,
 5-hydroxy-N,N-dimethyltryptamin, ML-1035, ML10302,
 5-metoxytryptamin, Metoclopramide, Mosapride,
 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin),
 15 Prucalopride, R 076186, R 093877, Renzapride, RS 17017,
 RS 56532, RS 57639, RS 67333, RS 67506, RS 67532,
 SB 204070, SB 205149, SC-53116, SC-49518, SK-951,
 SDZ 216-454, SR59768, TKS159, VB20B7, YM-47813, YM-53389,
 YM-09151, Zacopride, Zelmec and derivatives and pharma-
 20 ceutically acceptable salts thereof having essentially
 the same relaxing effect, in the manufacture of a medica-
 ment for therapeutic or prophylactic treatment of disor-
 ders involving bronchocontraction, wherein said agonist

7.

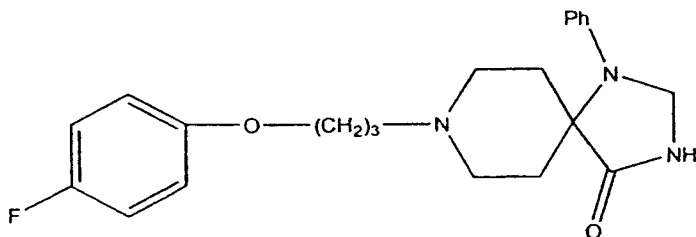
has the capacity of reducing the bronchocontraction by at least 30%, preferably at least 60%, most preferably at least 90%.

According to the present invention several known antagonist compounds are, surprisingly, able to influence the 5-HT_{2a} receptor, thereby generating a contraction reducing effect, i.e. a relaxation effect, and are selected from a group comprising ketanserin, AMI-193 or MDL 100 907, and derivatives and pharmaceutically acceptable salts thereof having the same or essentially the same contraction reducing effect.

Thus, the invention also relates to the use of one or more of the above-mentioned compounds, namely: ketanserin, i.e. 7-azido-3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-6-iodo-2,4(1H, 3H)-Quinazolinedione, having the structural formula:



AMI-193, i.e. 8-[3-(4-fluorophenoxy)propyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one, having the structural formula:



and ALEPH-2, Amperozide, amesergide, Aryloxyalkylimidazolines, 1-aryl-4-propylpiperazines, BIMT 17, 1-3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-6-fluoroindolin-2(1 H)-one, CGS 18102A, Clonidine, Cyproheptadine, Deramciclone, Desmethyl-WAY 100635, dotarizine, DV 7028, Elymo-

clavine, Fananserin, 8-[3-(4-fluorobenzoyl)propyl]-1-methyl-1,3,8-triazaspiro[4,5]decan-4-one, FG5893 hydrochloride, FG5974, FG5983, Hexahydrocarbazoles, (3H)WAY 100635, ICI169,369, 8-[3-(4-iodobenzoyl)propyl]-1-methyl-1,3,8-triazaspiro[4,5]decan-4-one, Ketanserin, LEK-8804, 5 LSD, LU 111995, (S,S)-LY-53,857, (R,S)-LY-53,857, (S,R)-LY-53,857, (R,R)-LY-53,857, LY-53,857 free base, LY 215840, MDL-11,939, MDL 28133A, MDL 100,151, MDL 100,907, mesulergine, Metergoline, 1-3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl indolin-2(1H)-one, 10 methysergide, Mianserin, NE-100, Nefazodone, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, NRA0045, Olanzapine, Ondansetron, 1-(2-pyrimidinyl)piperazine derivatives, Pizotifen, raclopride, Roxindole, Risperidone, 15 Ritanserin, RP62203, sarpogrelate and its active metabolite (M-1), serotonin reuptake inhibitors like fluoxetine, YM 992, medifoxamine, cericlamine, imipramine, iprindole, BIMT 17, citalopram, paroxetine, sertraline, fluvoxamine 20 spiro indoles N-substituted with a 3-(dimethylamino)-propyl chain Spiperone, SR 46349B, WAY 100635, WY-50,324, MDL 100,907, and derivatives and pharmaceutically acceptable salts thereof having essentially the same contraction reducing effect, in the manufacture of a medicament 25 for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said antagonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most 30 preferably at least 90%.

Ketanserin is excluded from the embodiment concerning the 5-HT_{2a} receptor antagonist compound for use as a medicament.

The present invention also relates to a method for 35 treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of the

compound according to the present invention having agonist activity to the 5-HT₄ receptor. Preferably, said method relates to the treatment of asthma and disorders related thereto.

5 The present invention also relates to a method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound according to the present invention having an-
10 tagonist activity to a 5-HT_{2a} receptor. Preferably, said method relates to treatment of asthma and disorders related thereto.

 Further, the present invention relates to a method for treatment of disorders involving bronchocontraction,
15 wherein the above-mentioned combination of agonist(s) and antagonist(s) is administered.

 The expression "has the capacity of reducing the pathological bronchocontraction by at least ...%" used throughout the present patent application means that the
20 compound in question reduces the contraction in the airways caused (1) either by the underlying disease (asthma etc) or (2) by the administration of 5-HT or other substances with 5-HT_{2a}-activating properties. The level of contraction in the airways can, for instance, be deter-
25 mined by spirometric measurements of the Forced Expiratory Volume (FEV₁), compared to the normal value for healthy people. Alternatively, the expiratory capacity for a patient can be compared to his own FEV₁ during periods of relatively little obstructive problems.

30 As appears from Fig. 1, the contractile component often manifests itself as a reduction or a complete elimination of the 5-HT induced relaxation, rather than in an increase of force from the control (pre-exposure) level. In the case of "specific" agonists to the 5-HT₄
35 receptor, this sustained relaxing effect is achieved because the contractile 5-HT_{2a} receptor is not affected; only the relaxing 5-HT₄ receptor is activated. In the

case of antagonists to the 5-HT_{2a} receptor, this effect is achieved due to direct blocking of the 5-HT_{2a} receptor, whereby the unspecific agonists to the 5-HT₄ receptor, such as 5-HT, can act without also causing contraction by the 5-HT_{2a} receptor.

It should be noted that the medicament prepared according to present invention in each embodiment may optionally include two or more of the above outlined compounds.

Further, in the embodiment when the compound having 5-HT_{2a} antagonist activity is administered, optionally together with complementary serotonin or derivatives thereof, a serotonin uptake inhibitor can be added with a view to amplifying the relaxing effect.

The typical daily dose of the medicament prepared according to the invention varies within a wide range and will depend on various factors such as the individual requirement of each patient and the route of administration.

Said medicament may be prepared as a composition adapted either for administration via the respiratory tract or for oral, intravenous, topical, intraperitoneal or subcutaneous administration, in association with one or more pharmaceutically acceptable carriers, diluents or adjuvants that are well known in the art.

Moreover, said medicament is preferably administered via the respiratory tract in the form of e.g. an aerosol or an air-suspended fine powder. However, in some cases a useful alternative to administration via the respiratory tract may be oral, topical, parenteral, subcutaneous, transdermal or rectal administration, wherein e.g. tablets, capsules, powders, microparticles, granules, syrups, suspensions, solutions, transdermal patches or suppositories are utilized.

Brief Description of the Drawing

Fig. 1 depicts the effects of 5-HT and selective 5-HT₄ agonists on the spontaneous tone in human in vitro

preparations. Note that 5-HT only gives a transient relaxation, while selective 5-HT₄ agonists give a strong sustained relaxing effect.

Detailed Description

5 The subject-matter of the present invention was inter alia deduced from animal experiments, where a specific behavior of the airway smooth muscle called "spontaneous tone" was examined. The spontaneous tone, which involves a spontaneous continuous contraction in
10 the airway smooth muscle, was studied due to a suspicion that defective regulation of the spontaneous tone could be an important cause of the bronchoconstriction observed in asthmatic patients.

 The examinations of the spontaneous tone were per-
15 formed in accordance with the methods disclosed in the thesis "*Regulation of spontaneous tone in guinea pig trachea*" by S.Skogvall, Department of Physiological Sciences, Lund University, 1999, which is incorporated herein by reference. As evidenced by these examinations,
20 the airways normally display a highly regular type of oscillating tone if exposed to physiological conditions, and the oscillating tone can be reversibly affected by administration of various substances. When the epithelium is removed, the preparations instead display a strong,
25 smooth type of tone.

 In short, the animal experiments in said thesis showed that the spontaneous tone to a large degree is controlled by powerful regulating factors released from neuroepithelial endocrine (NEE) cells.

30 Later experiments, not included in the thesis, have revealed that one of the regulating factors is serotonin, also called 5-HT, which exerts agonist action on the receptors 5-HT₁, 5-HT₄, 5-HT₅, 5-HT₆ and 5-HT₇, as well as on 5-HT₂ receptors.

35 Additional experiments have shown that when 1 μ M serotonin was added to denuded airway smooth muscle preparations from the guinea-pig displaying a strong, smooth

spontaneous tone, the average force level was increased significantly, i.e. a contraction was observed. A contractile effect of serotonin on airway smooth muscle has been reported in e.g. Skogvall, S., Korsgren, M., Grampp, W., *J. Appl. Phys.*, 86:789-798, 1999. However, when 10 μ M of serotonin was added, the spontaneous tone was significantly suppressed to a level of about half the force observed in control (drug-free) conditions. The spontaneous tone returned to approximately its normal level when the preparations were again exposed to control conditions. Thus, it has now surprisingly been shown that serotonin brings about contraction of the airways at low concentrations and relaxation at high concentrations, consequently having a dual effect on the airways.

Furthermore, it has been shown that when the contracting 5-HT_{2a} receptor was blocked with ketanserin, the 5-HT, i.e. serotonin, induced almost no contraction, but instead only a significant relaxation. Similar experiments have also been performed on human in vitro preparations, from patients undergoing lobectomy or pneumectomy due to lung cancer. It was found that in this tissue, 5-HT was even more potent in relaxing the airway smooth muscle than in guinea pig. In human tissue, already 1 μ M 5-HT induces a significant relaxation of the spontaneous tone.

Human airways are generally considered to display only a weak contraction when exposed to 5-HT. Nevertheless, examinations on spontaneous tone on human in vitro preparations have shown that 5-HT indeed has a contractile component also in this tissue. However, this contraction takes a longer time to develop than in guinea pig and the contractile effect is seen as a termination of the relaxation, rather than an increase of tone from the baseline. In guinea pig trachea, the contraction reaches a maximum after approximately 10 min, and this is followed by a considerable reduction of tone. However, human preparations instead induce a maximum relaxing ef-

fect after 5-10 min, which disappears gradually during the following 30-45 min (see Fig 1). The transient nature of the 5-HT relaxation is most likely caused by a simultaneous activation of the fast, relaxing 5-HT₄ receptor, and a slower activation of the contracting 5HT_{2a} receptor. This is clear, because activation of the relaxing 5-HT₄ receptor by a substance that lacks 5-HT_{2a} receptor activating properties (such as 5-carboxiamidotryptamine or SC 53116), results in a relaxation that is persistent and not transient (see Fig. 1).

It has previously been suggested that 5-HT or 5-HT analogues may be useful in the treatment of bronchoobstructive diseases. In SU 1 701 320 it is suggested that the 5-HT, i.e. serotonin, may be of use as an addition to standard beta2 receptor stimulation. However, from our experiments it seems clear that 5-HT is not effective or useful as the only treatment for e.g. asthmatic disorders, because of the transient relaxing effect by 5-HT (see Fig. 1). If instead, as we propose herein, a 5-HT analogue that lacks the 5-HT_{2a} activating properties is given, the relaxing effect is persistent, and not transient.

In summary, it has now been discovered that agonist action on the 5-HT₄ receptor results in a relaxing effect, whereas agonist action on 5-HT_{2a} receptors results in a contractile effect. In conclusion, the dual effect of serotonin is most likely a result of its agonist action on the relaxing 5-HT₄ receptor as well as on the contracting 5-HT_{2a} receptor.

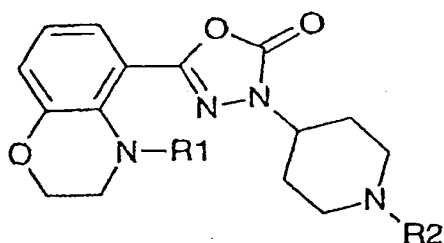
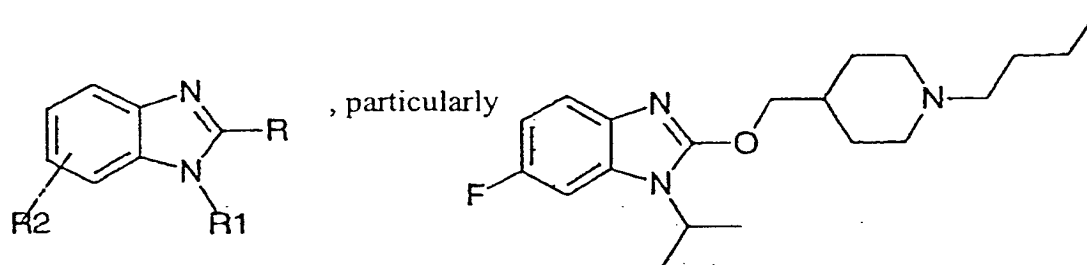
It was also deduced from these experiments that compounds having agonist activity to the 5-HT₄ receptor, while having only low or no agonist activity to a 5-HT_{2a} receptor, therefore are useful as agents for treatment of bronchocontraction disorders.

Thus, the present invention relates to the use of compounds having agonist activity to the 5-HT₄ receptor in the manufacture of a medicament intended for treatment

of bronchocontraction disorders, whereby said compounds have the strong bronchorelaxing effect of serotonin but have substantially no contractile effect. As mentioned above, the compounds used according to the present invention have only low or no agonist activity to 5-HT_{2a} receptors.

In the above mentioned experiments it has also been shown that compounds having antagonist activity to a 5-HT_{2a} receptor are useful as agents for treatment of bronchocontraction disorders, since they are capable of blocking the contractile effect of a compound having agonist activity to a 5-HT_{2a} receptor. The compounds according to the present invention having antagonist activity to the 5-HT_{2a} receptor may even be administered together with serotonin in the form of a complement to the serotonin content already present in the body with a view to obtaining an amplified contracting effect; or with any other substance having agonist activity to the 5-HT_{2a} receptor; or with a serotonin uptake inhibitor.

Said administration can be simultaneous or sequential, and a powerful relaxing effect on the bronchi can be achieved in this manner. Thus, the present invention also relates to the combined use of a compound having antagonist activity to a 5-HT_{2a}-receptor and a compound having agonist activity to the 5-HT₄ receptor, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction.

Further 5-HT₄ agonist structures useful according to the present invention

Arylcarbamate derivatives of 1-piperidineethanol
4-amino-5-chloro-2-methoxybenzoic acid esters,
e.g. ML10302, RS 57639 and SR59768

4-amino-5-chloro-2-methoxy-N-((2S,4S)-
1-ethyl-2-hydroxymethyl-4-
pyrrolidiny)benzamide, e.g. TKS159

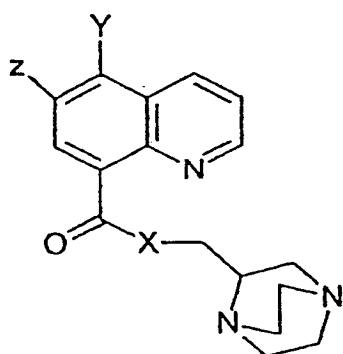
thiophene carboxamide derivatives 3 (a-j)

5. Azabicyclo(x.y.z) derivatives

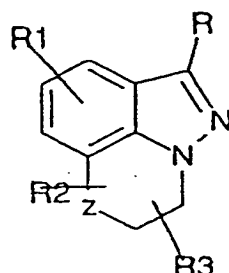
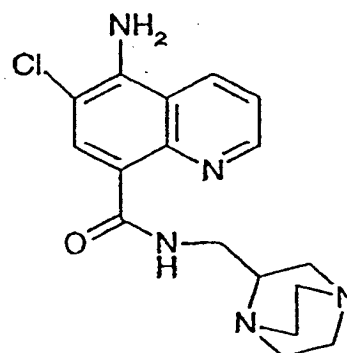
2-piperazinylbenzoxazole derivatives

2-piperazinylbenzothiazole derivatives, e.g. VB20B7
clebopride

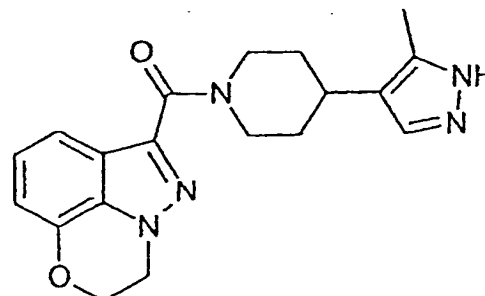
Sandoz compound 1b



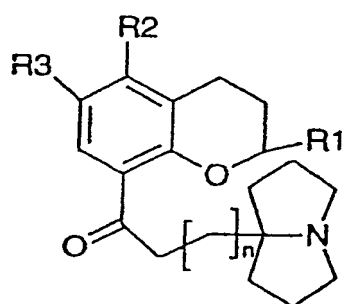
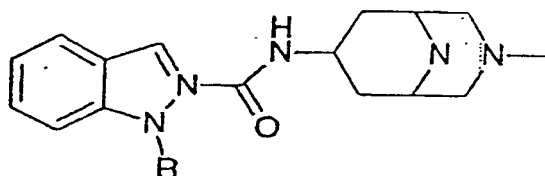
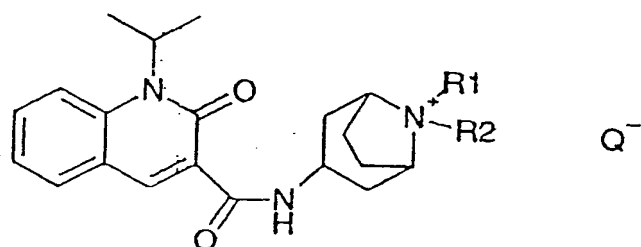
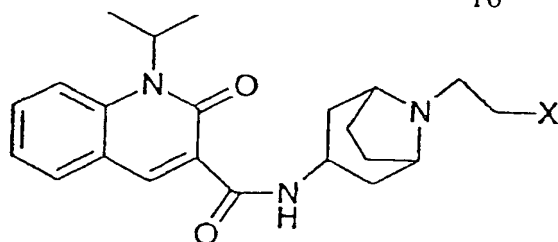
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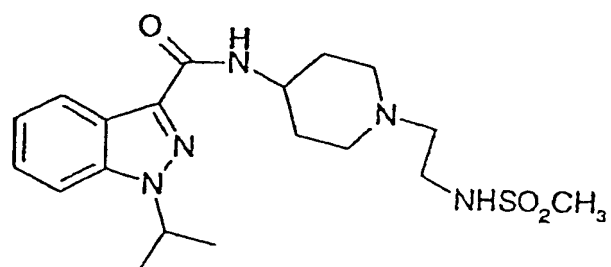
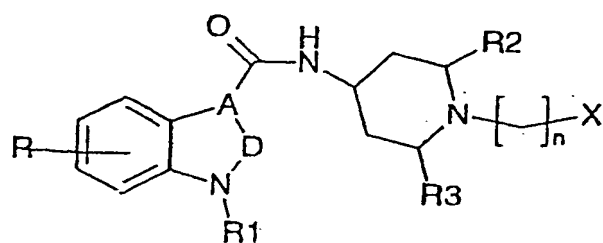
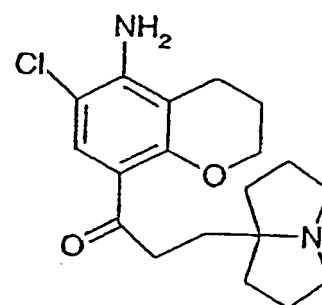
, particularly



16



, particularly



CLAIMS

1. Compound having agonist activity to a 5-HT₄ receptor, and derivatives and pharmaceutically acceptable salts thereof having agonist activity to the 5-HT₄ receptor for use as a medicament for treatment of disorders involving bronchocontraction.

2. Compound according to claim 1, wherein said compound has the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising 5-carboxamido-tryptamine, BIMU 1, BIMU 8, BRL 24924, Cisapride, DAU 6236, 5-hydroxy-N,N-dimethyltryptamin, ML-1035, ML10302, 5-metoxytryptamin, Metoclopramide, Mosapride, 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), Prucalopride, R 076186, R 093877, Renzapride, RS 17017, RS 56532, RS 57639, RS 67333, RS 67506, RS 67532, SB 204070, SB 205149, SC-53116, SC-49518, SK-951, SDZ 216-454, SR59768, TKS159, VB20B7, YM-47813, YM-53389, YM-09151, Zacopride and Zelmac.

3. Compound according to claim 2, wherein said bronchocontraction appears in asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia.

4. Use of one or more compounds according to claims 1 and 2 having agonist activity to a 5-HT₄ receptor, and derivatives and pharmaceutically acceptable salts thereof having agonist activity to the 5-HT₄ receptor, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, optionally together with a serotonin uptake inhibitor.

5. Use according to claim 4, wherein said one or more compounds has/have the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and
5 wherein said compound(s) is/are chosen from the group comprising 5-carboxamidotryptamine, BIMU 1, BIMU 8, BRL 24924, Cisapride, DAU 6236, 5-hydroxy-N,N-dimethyl-tryptamin, ML-1035, ML10302, 5-metoxytryptamin, Metoclopramide, Mosapride,
10 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), Prucalopride, R 076186, R 093877, Renzapride, RS 17017, RS 56532, RS 57639, RS 67333, RS 67506, RS 67532, SB 204070, SB 205149, SC-53116, SC-49518, SK-951, SDZ 216-454, SR59768, TKS159, VB20B7, YM-47813, YM-53389,
15 YM-09151, Zacopride and Zelmac.

6. Use according to claims 4 and 5, wherein said disorder having pathological bronchocontraction is asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or
20 various psychotic conditions including schizophrenia.

7. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound according to
25 claim 1.

8. Compound having antagonist activity to a 5-HT_{2a} receptor, and derivatives and pharmaceutically acceptable salts thereof having antagonist activity to the 5-HT_{2a} receptor for use as a medicament for treatment of disorders involving bronchocontraction.
30

9. Compound according to claim 8, wherein said compound has the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and
35 most preferably at least 90%, and wherein said compound is chosen from the group comprising AMI-193 and MDL 100,907,

and ALEPH-2, Amperozide, amesergide, Aryloxyalkylimi-
dazolines, 1-aryl-4-propylpiperazines, BIMT 17, 1-3-[4-
(3-chlorophenyl)-1-piperazinyl]propyl-6-fluoroindolin-2(1
H)-one, CGS 18102A, Clonidine, Cyproheptadine, Deramci-
5 clane, Desmethyl-WAY 100635, dotarizine, DV 7028, Elymo-
clavine, Fananserine, 8-[3-(4-fluorobenzoyl)propyl]-1-
methyl-1,3,8-triazaspiro[4,5]decan-4-one, FG5893 hydro-
chloride, FG5974, FG5983, Hexahydrocarbazoles, (3H)WAY
100635, ICI169,369, 8-[3-(4-iodobenzoyl)propyl]-1-methyl-
10 1,3,8-triazaspiro[4,5]decan-4-one, Ketanserin, LEK-8804,
LSD, LU 111995, (S,S)-LY-53,857, (R,S)-LY-53,857,
(S,R)-LY-53,857, (R,R)-LY-53,857, LY-53,857 free base,
LY 215840, MDL-11,939, MDL 28133A, MDL 100,151,
MDL 100,907, mesulergine, Metergoline, 1-3-[4-(2-
15 methoxyphenyl)-1-piperazinyl]propyl indolin-2(1H)-one,
methysergide, Mianserin, NE-100, Nefazodone,
N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, NRA0045,
Olanzapine, Ondansetron, 1-(2-pyrimidinyl)piperazine de-
rivatives, Pizotifen, raclopride, Roxindole, Risperidone,
20 Ritanserin, RP62203,
sarpogrelate and its active metabolite (M-1),
serotonin reuptake inhibitors like fluoxetine, YM 992,
medifoxamine, cericlamine, imipramine, iprindole, BIMT
17, citalopram, paroxetine, sertraline, fluvoxamine
25 spiro indoles N-substituted with a 3-(dimethylamino)-
propyl chain
Spiperone, SR 46349B, WAY 100635, WY-50,324, .

10. Compound according to claim 9, wherein said
bronchocontraction appears in asthma and disorders re-
30 lated thereto, emphysema, chronic bronchitis, chronic ob-
structive pulmonary disease, depression, anorectic or bu-
limic eating disorders, anxiety or various psychotic con-
ditions including schizophrenia.

11. Use of one or more of the compounds according to
35 claims 8 and 9 and including ketanserin having antagonist
activity to a 5-HT_{2a} receptor, and derivatives and pharma-
ceutically acceptable salts thereof having antagonist ac-

tivity to the 5-HT_{2a} receptor, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, optionally together with a serotonin uptake inhibitor.

- 5 12. Use according to claim 11, wherein said one or more compounds has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound(s) is/are chosen from the group comprising
- 10 ketanserin, AMI-193, MDL 100,907
and ALEPH-2, Amperozide, amesergide, Aryloxyalkylimidazolines, 1-aryl-4-propylpiperazines, BIMT 17, 1-3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-6-fluoroindolin-2(1H)-one, CGS 18102A, Clonidine, Cyproheptadine, Deramciclane, Desmethyl-WAY 100635, dotarizine, DV 7028, Elymoclavine, Fananserin, 8-[3-(4-fluorobenzoyl)propyl]-1-methyl-1,3,8-triazaspiro[4,5]decan-4-one, FG5893 hydrochloride, FG5974, FG5983, Hexahydrocarbazoles, (3H)WAY 100635, ICI169,369, 8-[3-(4-iodobenzoyl)propyl]-1-methyl-1,3,8-triazaspiro[4,5]decan-4-one, Ketanserin, LEK-8804, LSD, LU 111995, (S,S) -LY-53,857, (R,S) -LY-53,857, (S,R) -LY-53,857, (R,R) -LY-53,857, LY-53,857 free base, LY 215840, MDL-11,939, MDL 28133A, MDL 100,151, MDL 100,907, mesulergine, Metergoline, 1-3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl indolin-2(1H)-one, methysergide, Mianserin, NE-100, Nefazodone, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, NRA0045, Olanzapine, Ondansetron, 1-(2-pyrimidinyl)piperazine derivatives, Pizotifen, raclopride, Roxindole, Risperidone, Ritanserin, RP62203, sarpogrelate and its active metabolite (M-1), serotonin reuptake inhibitors like fluoxetine, YM 992, medifoxamine, cericlamine, imipramine, iprindole, BIMT 17, citalopram, paroxetine, sertraline, fluvoxamine spiro indoles N-substituted with a 3-(dimethylamino)-propyl chain
- 35 Spiroperone, SR 46349B, WAY 100635, WY-50,324, .

13. Use of one or more compounds according to claims 11 and 12 in combination, either simultaneously or sequentially, with a compound having agonist activity to the 5-HT₄ receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, optionally together with a serotonin uptake inhibitor.

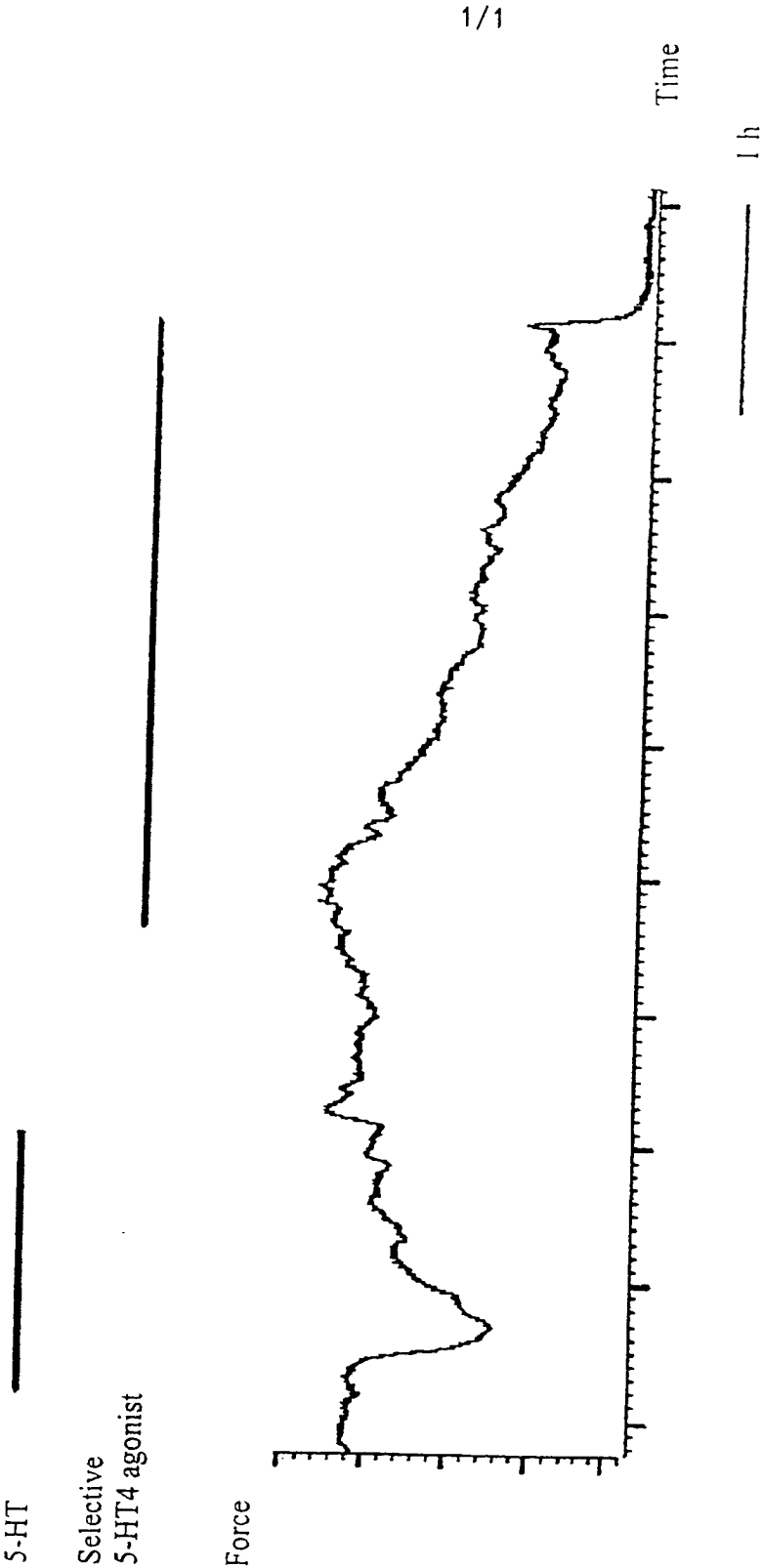
14. Use according to claim 13, wherein said compound having agonist activity to the 5-HT₄ receptor is serotonin and derivatives thereof or a compound according to claims 1 and 2.

15. Use according to claims 11-14, wherein said disorder having pathological bronchocontraction is asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia.

16. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound according to claims 11-14.

17. Composition comprising a combination of the compounds defined in claims 13 and 14 for use as a medicament for treatment of disorders involving bronchocontraction.

Fig 1



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/00819

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7, 16
because they relate to subject matter not required to be searched by this Authority, namely:
**A method for treatment of the human or animal body by therapy,
see rule 39.1.**
2. ☒ Claims Nos.: 1-6, 8-15, 17
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
See extra sheet.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/00819

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5418241 A (SAMIR JEGHAM ET AL), 23 May 1995 (23.05.95) --	
A	WO 9717345 A1 (SYNTHELABO), 15 May 1997 (15.05.97) --	
A	STN, International, File CA, Chemical Abstracts, volume 117, no. 7, 17 August 1992 (Columbus, Ohio, US), Taivan, I.L. et al: "Method for stopping bronchial asthma attack"; & 63015, SU,A1,1701320, 19911230 -- -----	

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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17 August 2000

Date of mailing of the international search report

29 -08- 2000

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/00819

The claims are of a plurality of different categories and contain a plurality of alternatives and parameters which render it difficult, if not impossible to determine the matter for which protection is sought. The present application therefore fails to comply with the clarity and conciseness requirements of Article 6 PCT to such an extent that a meaningful search on the basis of the claims is impossible.

Expressions such as "compound ... having agonist activity to a 5-HT₄ receptor" are unclear and defined in terms of the result to be achieved. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. Further, expressions such as "disorders involving bronchocontraction" and "derivatives" are not clear and concise.

Due to the complexity of the claims, a search has been carried out for those parts of the claims which appear to be supported and disclosed, namely the part of claim 4 which refers to claim 2. The search has been aimed at documents having explicit information of use for treatment of bronchocontraction.

The applicants attention is drawn to the fact that claims relating to inventions in which no international search report has been established will not be the subject of an international preliminary examination (Rule 66.1(e) PCT). This is the case irrespective of whether or not the claims are amended following receipt of the search report during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE 00/00819

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		FR 2741070 A,B	16/05/97
		FR 2745574 A,B	05/09/97

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(10) International Publication Number
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- (51) International Patent Classification⁷: **A61K 31/395**, **A61P 11/08** (74) Agent: AWAPATENT AB; Box 5117, S-200 71 Malmö (SE).
- (21) International Application Number: **PCT/SE00/00819** (81) Designated States (*national*): AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (22) International Filing Date: **28 April 2000 (28.04.2000)**
- (25) Filing Language: **English**
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- (30) Priority Data:
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|------------|----------------------------|----|
| 9901531-5 | 28 April 1999 (28.04.1999) | SE |
| 60/131,355 | 28 April 1999 (28.04.1999) | US |
| 9901906-9 | 26 May 1999 (26.05.1999) | SE |
| 60/136,604 | 27 May 1999 (27.05.1999) | US |
| 9902251-9 | 15 June 1999 (15.06.1999) | SE |
| 9902252-7 | 15 June 1999 (15.06.1999) | SE |
| 60/139,632 | 17 June 1999 (17.06.1999) | US |
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- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— With international search report.
- (71) Applicant (*for all designated States except US*): **RESPIRATORIUS AB [SE/SE]**; Sölvegatan 41, S-223 70 Lund (SE).
- (72) Inventor; and
- (75) Inventor/Applicant (*for US only*): **SKOGVALL, Staffan [SE/SE]**; Flygelvägen 33, S-224 72 Lund (SE).
- (88) Date of publication of the international search report:
14 June 2001
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: **COMPOUND FOR USE AS A MEDICAMENT FOR TREATMENT OF DISORDERS INVOLVING BRONCHOCONTRACTION**

(57) Abstract: The present invention relates to a compound having agonist activity to the 5-HT₄ receptor for use as a medicament and to the use of said compounds in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compounds are administered. The present invention also relates to a compound having antagonist activity to the 5-HT_{2A} receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compounds are administered.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/00819

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/395, A61P 11/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5418241 A (SAMIR JEGHAM ET AL), 23 May 1995 (23.05.95) --	4-6
A	WO 9717345 A1 (SYNTHELABO), 15 May 1997 (15.05.97) --	4-6
A	STN, International, File CA, Chemical Abstracts, volume 117, no. 7, 17 August 1992 (Columbus, Ohio, US), Taivan, I.L. et al: "Method for stopping bronchial asthma attack"; & 63015, SU,A1,1701320, 19911230 --	4-6

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"&" document member of the same patent family

Date of the actual completion of the international search

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Date of mailing of the international search report

26 -03- 2001

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Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/00819

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, Volume 111, No 15, 9 October 1989 (09.10.89), (Columbus, Ohio, USA), Tsuchiya, Yoshio et al, "Inhibition of the vagal reflex-induced tracheal constriction by psychotropic drugs", page 61, THE ABSTRACT No 126896a, J. Pharmacobio-Dyn. 1989, 12 (7), 437-440 --	12
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X	British Journal of Pharmacology, Volume 124, 1998, J.J. De Bie et al, "Modulation of airway hyperresponsiveness and eosinophilia by selective histamine and 5-HT receptor antagonists in a mouse model of allergic asthma" page 857 - page 864 --	12

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/00819

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chinese Journal of Physiology, Volume 32, No 1, 1989, Shang-Jyh Kao et al, "The Effects of alpha2-Adrenergic Agonism with Clonidine on the Pulmonary Collateral Resistances in the Canine Lung Challenged with Histamine" page 21 - page 29 --	12
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A	EP 0797995 A2 (ELI LILLY AND COMPANY), 1 October 1997 (01.10.97) --	12
X	European Neuropsychopharmacology, Volume 8, 1998, John P. Redrobe et al, "Clonidine potentiates the effects of 5-HT1A' 5-HT1B and 5-HT2A/2C antagonists and 8-OH-DPAT in the mouse forced swimming test" page 169 - page 173 --	17
X	J Neural Transm (GenSect), Volume 83, 1991, M. L. Wadenberg et al, "Antipsychotic-like profile of combined treatment with raclopride and 8-OH-DPAT in the rat: enhancement of antipsychotic-like effects without catalepsy" page 43 - page 53 --	17

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/00819

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Anti-Cancer Drugs, Volume 7, 1996, Vittorio Gebbia et al, "Treatment of cisplatin-related nausea and vomiting with a combination of ondansetron and metoclopramide: a pilot study" page 734 - page 737 --	17
X	British Journal of Pharmacology, Volume 122, 1997, R. W. Clarke et al, "Enhancement and depression of spinal reflexes by 8-hydroxy-2-(di-n-propylamino)tetralin in the decerebrated and spinalized rabbit: involvement of 5-HT1A-and non-5-HT1A-receptors" page 631 - page 638 --	17
X	Acta pharmacol. et toxicol., Volume 55, 1984, Jorn Arnt et al, "The Citalopram/5-HTP-induced Head Shake Syndrome is Correlated to 5-HT2 Receptor Affinity and also Influenced by other Transmitters" page 363 - page 372 --	17
X	Anticancer Research, Volume 17, 1997, Giorgio Mustacchi et al, "The Combination of Metoclopramide, Methylprednisolone and Ondansetron Against Antiblastic-Delayed Emesis: A Randomised Phase II Study" page 1345 - page 1348 -- -----	17

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **1-6, 8-15 and 17**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☒ Claims Nos.: **7 and 16**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
A method for treatment of the human or animal body by therapy,
see rule 39.1
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Box I.1

The claims contain a plurality of different compounds and parameters which render it difficult, if not impossible to determine the matter for which protection is sought. The present application therefore fails to comply with the clarity and conciseness requirements of Article 6 PCT to such an extent that a meaningful search of the whole scope of the claims is impossible.

Expressions such as "compound ... having agonist activity to a 5-HT4 receptor" are unclear and defined in terms of the result to be achieved. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. Further, expressions such as "disorders involving bronchocontraction" and "derivatives" are not clear and concise.

Due to these deficiencies, a search has been carried out for those parts of the claims which appear to be supported and disclosed, namely the part of claim 4 which refers to claim 2 (invention 1), the part of claim 12 which refers to claim 11 (invention 2) and the combination of the compounds according to claims 4 and 12 (invention 3).

The search has been aimed at documents having explicit information of use for treatment of bronchocontraction.

The applicants attention is drawn to the fact that claims relating to those parts of the inventions in which no international search report has been established will not be the subject of an international preliminary examination (Rule 66.1(e) PCT). This is the case irrespective of whether or not the claims are amended following receipt of the search report during any Chapter II procedure.

Box II

As is stated in Annex B to Administrative Instructions under the PCT, in force July 1, 1998, (PCT GAZETTE 1998, June 25, pp 45-50) unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features"- i.e. features that define a contribution which each of the inventions makes over the prior art (cf. PCT Rule 13.2). It is well known to a person skilled in the art, that compounds with 5-HT4 receptor agonist activity have pharmaceutical use. This leads to the presence of the subjects listed below, each falling under its own restricted inventive concept.

Invention 1. Claims 1-7 relating to a compound having agonist activity to a 5-HT4 receptor.

Invention 2. Claims 8-12 relating to a compound having antagonist activity to a 5-HT2a receptor.

Invention 3. Claims 13-17 relating to a composition comprising a combination of compounds.

INTERNATIONAL SEARCH REPORT
Information on patent family members

25/02/01

International application No.
PCT/SE 00/00819

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25/02/01

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